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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,357	03/21/2001	De-Chao Yu	348022001600	3927

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,357	YU ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-76* is/are pending in the application.

4a) Of the above claim(s) *64 and 67-71* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-63,65,66 and 72-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/15/01* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,12* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *14* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 59-63, 65-66, and 72-76 are pending examination.

Election of Group I, claims 1-51 and 55-58 and species: alkaloids, adenoviral gene essential for replication (early gene), radiation therapy (external radiation); cell specific TRE (PSA-TRE) in paper no. 13 is acknowledged and are considered to be made without traverse because applicants did not point out the error(s) to the election/restriction set forth in paper no. 11.

However, claims 1-58 were cancelled in paper no. 16 and new claims 59-76 were added.

Therefore, the elected group and elected species from paper no. 13 will be directed to the new claims.

Claims 64 and 67-71 and the non-elected anti-neoplastic agents (5-fluorouracil, mitoxanthrone) and the non-elected TRE are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 16.

The preliminary amendment in paper nos. 8 and 10 is acknowledged and entered.

Information Disclosure Statement

The WO documents were not initialed on paper no. 9 because the documents were already cited on another 1449 (See paper no. 12).

The international search report has been considered.

Drawings

NOTE: In the next response, please submit a response to the PTO 498 because a PTO 498 was filed with the office dated 5/31/02 paper no. 11 and the applicants have not submitted proposed corrections to the drawings. If the reply to the Non-Final Rejection does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Claim Objections

Claims 59, 62, 63, 65, 66, and 76 are objected to because of the following informalities: Claim 59 is missing a period at the end of the claim. Claim 62 encompasses a non-elected species (antimetabolites, 5-fluorouracil). Claims 63 and 66 do not further limit claim 59 because they are based on a claim with closed language "consisting of at least one anti-neoplastic agents selected of the group consisting of". Both claims list alkaloids (etoposide in claim 63 or estramustine in claim 66) that were not listed in the "group consisting of" in the independent claim. Claim 62 encompasses a non-elected species (antibiotic, mitoxantrone). Claim 76 does not refer to a preceding claim and refers to a claim that is not part of the listed claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-63, 65-66, and 72-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method for suppressing tumor growth in a mammal comprising: directly administering to a tumor of a mammal a target cell-specific

adenovirus vector, wherein said vector comprising an adenovirus gene essential for replication under transcriptional control of a transcriptional regulatory element (TRE) and administering an effective amount of an alkaloid to the mammal for suppressing tumor growth when administered; 2) A method for suppressing tumor growth in a mammal comprising: directly administering to a tumor in a mammal a target cell-specific adenovirus vector, wherein said vector comprising an adenovirus gene essential for replication under transcriptional control of a TRE and administering an effective amount of radiation to the mammal for suppressing tumor growth when administered, and does not reasonably provide enablement for the full scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is a method of treating neoplasia in an individual using combination of target cell-specific replication competent adenoviral vector and chemotherapy or radiation therapy. The invention lies in the field of gene therapy.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy

method to be successful (page 238, columns 1 and 2). Thus, the state of the art of gene therapy is considered highly unpredictable.

The as-filed specification describes several experiments to determine which combination of adenovirus and chemotherapy or radiation therapy suppresses tumor growth in mice (pages 102-166). The specification displays in vitro and in vivo data for tumor suppression (tumor grown on mice) using different chemotherapies with a cell specific adenoviral vector (See tables 5, 6, 7, 8).

The disclosure provides sufficient guidance for how these experiments reasonably correlate to an *in vivo* method of gene therapy for suppressing tumor growth in a mammal comprising direct administration to said mammal with a replicant competent adenoviral vector in combination with chemotherapy or radiation therapy. However, these experiments do not reasonably correlate to any other *in vivo* method of cancer gene therapy for suppressing tumor growth in a mammal using intravenous, intraperitoneal, dermal, nasal, buccal, rectal, vaginal, or topical administration of said adenoviral vector. In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to

compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).

Vile further discusses:

A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

In view of the concerns set forth by the state of the art for any route of administration, the as-filed specification does not reasonably address the concerns put forth by the state of the art for cancer gene therapy concerning any route of administration other than direct administration. The claimed adenoviral vector used in the claimed invention depends on destroying the cancer cells be replicating in the cells and does not require a heterologous gene (thymidine kinase, cytosine deaminase, etc.). Therefore, in view of the art of record, the as-filed specification does not provide sufficient guidance for how one skilled in the art can administer the adenoviral vector in

a sufficient amount using any route other than direct so that the vector can efficiently destroy the cells. Furthermore, in view of the lack of a step in the claims for where the adenovirus vector is being administered it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the claims to what route of administration the claims encompass. Thus, the as-filed specification is only enabled for direct administration.

The state of the art for a vector in anti-cancer gene therapy as exemplified by Vile et al., *Gene Therapy*, Vol. 7, pp. 3, 2000. Vile teaches:

> To date, cancer gene therapy trials have variously used the three most common vectors (plasmid, retrovirus, and adenovirus). However, except for the situation where tumor/immune cells are manipulated ex vivo, there will be a clear preference in the coming years for the use of adenoviral vector for in vivo delivery to tumors. Dominant (10^{11} p.f.u./ml) compared with other vectors. The initial rationale of the use of C-type retroviral vectors to target exclusively dividing tumor cells on the background of a quiescent tissue is being gradually superseded by the realization that human tumors generally cycle much more slowly than the rodent cell lines on which the strategy was based.
>
> However, even the highest titer system is clearly not high enough yet to cure even local tumors. Therefore, there is a clear need to explore and exploit, a range of alternative options. Other systems, such as AAV and HSV, are already well developed for use in other gene therapy contexts and may be valuable in certain conditions within the cancer area.

> The development of replication vectors for cancer gene therapy is the inevitable consequence of data from the early clinical trials. So far, a substantial therapeutic gap still exists between the overlap of the efficacy provided by, on the other hand, the potency of the therapeutic gene(s) and on the other, the efficiency of gene delivery provided by the vector. Only when these two 'therapeutic domains' approach each other will clinical efficacy result.

In addition, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration would result in a therapeutic response using the replication competent adenoviral vector. The specification displays directly administering said vector to a tumor on a mouse. The state of the art for the route of administration for gene therapy as exemplified by Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In view of the state of the art, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to any other route of administration to generate a therapeutic response in any individual with cancer.

In addition, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of mammal to the full scope of the claimed invention that would generate a treatment of any type of tumor in any individual (*e.g.* birds, fish,

mammals, etc.) with cancer. Since the state of the art cites that "the spontaneous behavior of human tumors is somewhat different for that of malignant cells in vitro, and from that of experimental tumors in animal models" (Gomez-Navarro et al., *European Journal of Cancer*, Vol. 35, pp. 868, Table 1, 1999). Even if a therapeutic response using an in vivo method of gene therapy for cancer in an experimental murine model using direct administration of a recombinant replicant competent adenoviral vector has been shown in the specification, it is not apparent as to how it is reasonably extrapolated to the full scope of the claimed invention, encompassing treating any type of cancer in an individual other than a mammal.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made provide enablement for 1-2, listed above. However, the rest of the disclosure encompassing any *in vivo* method of gene therapy in any individual is not enabled. Given that gene therapy wherein any adenoviral vector was employed to correct a disease or a medical condition in any individual was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy method for treating any type of cancer in any individual, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 59-63, 65-66, and 72-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59-63, 65-66, and 72-75 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is: what is the target of the adenovirus vector and how is the adenovirus vector suppressing tumor growth in an individual if the claim does not define where it is being administered. The claim is indefinite because the claim does not complete the pre-amble, which encompasses a method for suppressing tumor growth in an individual.

The phrase "administered is less than that known in the art to be effective for suppressing tumor growth when administered alone" in claims 59-63, 65-66, 72-75 is a relative term, which renders the claims indefinite. The term "administered is less than that known in the art to be effective for suppressing tumor growth when administered alone" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bound of the phrase. More specifically, the phrase is relative to one skilled in the art and one skilled in the art would not know which amount is considered the standard because the claim does not particularly point and define what are the metes and bounds of the phrase.

Claim 76 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for not defining the metes and bounds of the claim because claim 76 is the last claim in the claimed invention and it refers to claim 77, which is not listed. Therefore, one skilled in the art cannot determine what are the metes and bounds of the claim. Clarification is requested.

Claim Rejections - 35 USC § 103

Note: claim 76 is not rejected under 103 because the examiner cannot determine what claim, claim 76 is dependent from. However, if applicants amend the claim to read on a pending claim, then the examiner will have to consider if the claim falls under one of the following 103 rejections or if a new rejection under 103 is required.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59, 61, 66, and 72-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with Kirn et al. (WO 99/59604, IDS). Henderson teaches a method for suppressing tumor growth comprising introducing an adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element comprising an enhancer for prostate specific antigen and a promoter into a tumor cell, wherein the introduction of the vector results in suppression of tumor growth (column 44, claim 30). Furthermore, Henderson teaches that the adenovirus gene essential for propagation is the adenoviral early gene, E1A or E1A and E1B (columns 10- 11 and column 15). However, Henderson does not specifically teach a method for suppressing tumor growth in a mammal comprising administering a replication competent adenoviral vector and at least one anti-neoplastic agent from the group consisting of paclitaxel, docetaxel, doxrubicin, and cisplatin.

However, at the time the invention was made, Kirn teaches a method for treating cancer consisting of a combination of adenoviral vector and cisplatin (alkaloid) at 80 mg/m2 (abstract and pages 9, 11, and 13). Kirn teaches using an amount of cisplatin that is contemplated by the specification (see pages 49-50 of the specification for the concentration range of alkaloids used in chemotherapy).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use cisplatin in the method for suppressing tumor growth in a tumor taught by Henderson. One of ordinary skill in the art would have been motivated to use the combination of adenoviral vector and cisplatin in a method of suppressing tumor in a tumor cell because of the additive effect of using the combination to treat tumor cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 59, 60, 61, 62, 63, 65, 66, and 72-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with Gurnani et al. (Cancer Chemother. Phamacol., Vol. 44, pp. 143-151, 1999). Henderson teaches a method for suppressing tumor growth comprising introducing an adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element comprising an enhancer for prostate specific antigen and a promoter into a tumor cell, wherein the introduction of the vector results in suppression of tumor growth (column 44, claim 30). Furthermore, Henderson teaches that the adenovirus gene essential for propagation is the adenoviral early gene, E1A or E1A and E1B (columns 10- 11 and column 15). However, Henderson does not teach specifically teach a method using a replication competent adenoviral vector comprising administering to a tumor a target cell-specific adenovirus vector, wherein said vector comprises an adenoviral gene essential for replication under control of a target cell-specific TRE and an anti-neoplastic agent selected from the group consisting of doxorubicin, etoposide, cisplatin, wherein the amount of alkaloid is administered less than that known in the art to be effective for suppressing tumor growth when administered alone.

However, at the time the invention was made, Gurnani teaches that p53 adenovirus combined with cisplatin, doxorubicin, paclitaxel, methotrexate, or etoposide inhibited cell proliferation more effectively than chemotherapy alone (pages 145-150). Gurnani teaches using doxorubicin (4mg/kg), cisplatin (1mg/kg), etoposide at amounts that is contemplated by the

specification for suppressing tumor growth when administered alone (see pages 49-50 of the specification for the concentration range of alkaloids used in chemotherapy).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use any alkaloid taught by Gurnani in combination with the adenoviral vector taught by Henderson in a method for suppressing tumor growth in a tumor. One of ordinary skill in the art would have been motivated to use any alkaloid taught by Gurnani in combination with the adenovirus vector taught by Henderson in a method of suppressing tumor in a mammal because Gurnani teaches that the combination is more effective than chemotherapy alone.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 59, 73, and 74 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with Kirn et al. (WO 99/59604, IDS) in further view of Duque et al. (Cancer Gene Therapy, Vol. 6, pp. 554-563, 1999) or Henderson taken with Gurnani (Cancer Chemother. Phamacol., Vol. 44, pp. 143-151, 1999) in further view of Duque.

The rejection of the base claims 59 and 73 under 35 U.S.C. 103(a) is applied here as indicated above, by Henderson taken with Kirn or Henderson taken with Gurnani. However, Henderson taken with Kirn or Henderson taken with Gurnani does not teach specifically teach a method using a replication competent adenoviral vector comprising administering to a tumor a target cell-specific adenovirus vector, wherein said vector comprises an adenoviral gene essential for replication under control of a target cell-specific TRE and an alkaloid, wherein the gene essential for replication is the adenoviral early gene E1B with a deletion of the 19-kDa region.

However, at the time the invention was made, Duque teaches that 19-kDa and 55-kDa E1B-deficient adenovirus induced marked cytopathic effect on malignant cells that was higher than that seen for wild type adenovirus (abstract). In addition, such adenovirus exerts a tumor suppressor effect *in vivo*. Duque teaches the 19-kDa protein in adenovirus inhibits the apoptotic pathway induced by expression of the Ad E1a protein (page 555).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to modify the adenovirus used in the combination method for suppressing tumor growth in a tumor taught by Henderson taken with either Kirn or Gurnani. One of ordinary skill in the art would have been motivated to modify the adenovirus by deleting the 19-kDa region and using the modified vector in combination with cisplatin in a method of suppressing tumor in a tumor cell because Duque teaches that deleting the 19-kDa region can induce a higher cytopathic effect in malignant cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Henderson et al. (US Patent No. 5,871,726) taken with Chiang et al. (WO 97/10007, IDS). Henderson teaches a method for suppressing tumor growth comprising introducing an adenovirus vector comprising an adenovirus gene essential for propagation under transcriptional control of a prostate specific response element comprising an enhancer for prostate specific antigen and a promoter into a tumor cell, wherein the introduction of the vector results in suppression of tumor growth (column 44, claim 30). However, Henderson does not specifically teach a method for suppressing tumor

growth in a mammal comprising administering a replication competent adenoviral vector and an appropriate course of external radiation.

However, at the time the invention was made, Chiang teaches a process for improving the treatment of tumor by radiation therapy which comprises treating a tumor by radiation therapy wherein the cells have been transfected with a polynucleotide encoding a wild type p53, such as for example by transducing the cells with an adenoviral vector comprising a DNA sequence encoding wild-type p53 (abstract, pages 1, 3, 21, 34-37). Chiang teaches using radiation therapy that less is than that known in the art to be effective for suppressing tumor growth when administered alone (see page 160 of the as-filed specification).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the inventions was made to use external radiation in the method for suppressing tumor growth in a tumor taught by Henderson. One of ordinary skill in the art would have been motivated to use the combination of adenoviral vector and external radiation in a method of suppressing tumor in a tumor cell because of the additive effect of using the combination to treat tumor cells.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
10/21/02

DAVE T. NGUYEN
PRIMARY EXAMINER